The Role of Craving in Relapse After Discontinuation of Long-Term Benzodiazepine Use

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Objective: Craving for benzodiazepines has never been examined as a factor of relapse after successful benzodiazepine discontinuation. In this study, we examined the predictive value of craving on benzodiazepine relapse.

Method: A stepped-care intervention trial aimed to discontinue long-term benzodiazepine use in general practice. The first step was the sending of a letter to users advising them to gradually quit their use by themselves (i.e., minimal intervention). The second step, a supervised tapering-off program, was offered to those unable to discontinue by themselves. Craving was assessed by means of the Benzodiazepine Craving Questionnaire (BCQ). Multiple Cox proportional hazards regression analyses were performed to examine the effect of craving on subsequent relapse during a 15-month follow-up period in patients who had successfully quit their benzodiazepine use by themselves after the minimal intervention (N = 79) and in those patients who had successfully quit after the supervised tapering-off program (N = 45). Data were collected from August 1998 to December 2001.

Results: Thirty-five (44%) and 24 (53%) patients had relapsed after the minimal intervention and tapering-off program, respectively. Patients able to quit by themselves experienced very little craving. In this sample, craving was not related to relapse (p = .82). In patients who needed an additional supervised tapering-off program, higher craving scores were significantly related to relapse (hazard ratio = 1.26, 95% CI = 1.02 to 1.54, p = .029), when corrected for benzodiazepine characteristics, psychopathology, and personality characteristics.

Conclusion: Craving is an independent factor of subsequent relapse after successful benzodiazepine discontinuation in long-term benzodiazepine users who are not able to quit their usage of their own accord.

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Craving is generally considered an important variable in substance dependence. Empirical results, however, are not consistent, suggesting that craving is neither sufficient nor necessary for continued use or relapse to the use of addictive substances. (See, e.g., Drummond[1] for an overview.) The concept of craving has been studied frequently in substance dependence for various substances, but rarely in the case of benzodiazepine use. Although benzodiazepines have the potential to cause all aspects of dependence, even in low dosages,[2] only 1 study has examined the prevalence of benzodiazepine dependence according to ICD-10 and DSM-III-R criteria. That study found that approximately half of all benzodiazepine users in general practice met the criteria for benzodiazepine dependence.[3] Recently, the concept of craving for benzodiazepines has been examined within a benzodiazepine discontinuation project,[4,5] which has resulted in the development of the Benzodiazepine Craving Questionnaire (BCQ).[6] Up till now, benzodiazepine craving has never been examined prospectively in relation to

TAKE-HOME POINTS

- The Benzodiazepine Craving Questionnaire (BCQ) is a psychometrically sound instrument with which to assess craving for benzodiazepines.
- Clinicians should recognize craving as a potential risk factor for relapse after patients have successfully discontinued long-term, low-dose benzodiazepine use.
- Clinicians should explore the patients' expectations of the effects of benzodiazepines and focus on how to cope with craving.

benzodiazepine relapse after successful benzodiazepine discontinuation.

Several factors, e.g., benzodiazepine dosage, dependence characteristics, psychopathology, and personality, have been related to successful benzodiazepine discontinuation,[7–11] but almost exclusively they concern short-term outcome programs. Although 2 out of 3 patients successfully quit their use by means of these programs, relatively high relapse rates have been reported,[11,12] stressing the need to identify patients at risk for relapse. The only 2 studies[13,14] that have evaluated relapse after a supervised benzodiazepine tapering-off program have found treatment condition (cognitive-behavioral therapy for insomnia, a supervised medication taper program, or a combined approach), end-of-treatment insomnia severity and psychological distress (in the first study[13]), and self-efficacy in coping without benzodiazepines (in the second study[14]) as predictors of relapse. Two other studies have examined predictors of relapse in benzodiazepine users who had quit their use by themselves after receiving a letter advising them to discontinue their use. Baseline characteristics that predicted relapse in this population were a higher dosage, use of more than 1 benzodiazepine, lower general health perception, and hypnotic type benzodiazepine.[15,16]

This study was conducted to test the hypotheses that craving is an independent predictor of relapse in long-term benzodiazepine users who successfully quit their use after (1) a minimal intervention and (2) after an additional supervised benzodiazepine tapering-off program in general practice.

METHOD

Study Design and Participants

This study was conducted as part of a larger study on the efficacy of a stepped-care model aimed at reducing long-term benzodiazepine use in general practice in the Netherlands. Participants were long-term, benzodiazepine-using, general-practice patients from 30 general practices with 55 general practitioners (GPs). Long-term users were selected on the basis of the following criteria: (1) having received benzodiazepine prescriptions for at least 3 months and (2) having received prescriptions in an amount sufficient for at least 60 days in the 3 months prior to this study. Patients were excluded if benzodiazepine discontinuation could have a negative impact on their additional psychiatric treatment or underlying (major psychiatric) disorder (e.g., bipolar disorder or schizophrenia). For details on the exclusion criteria, see Figure 1.

The first step of the study was a minimal intervention strategy, i.e., a letter from the general practitioner advising patients to discontinue benzodiazepine use by themselves. Patients who had successfully quit their benzodiazepine use by themselves after receiving this letter were the first group of interest for the present study. Patients who had continued benzodiazepine consumption after this intervention were approached to participate in the consecutive, more intensive step, i.e., a randomized, controlled benzodiazepine discontinuation trial with 3 conditions: (1) tapering off alone, (2) tapering off with simultaneous group cognitive-behavioral therapy, and (3) a usual-care control group. Patients who had successfully quit their usage after participation in one of the 2 active conditions of this randomized, controlled trial were the second group of interest for the present study. Since patients in both active treatment conditions were equally successful, with similar rates of relapse, this group was treated as one cohort.[11,12] Written informed consent was obtained from all participants after full explanation of the study procedures.

The study received ethical approval from the Radboud University Nijmegen Medical Centre and was carried out between August 1998 and December 2001. It has been described in detail previously.[4,5] Figure 1 presents the recruitment process for the present study.

Measurements

The use of benzodiazepines and other prescribed drugs was monitored prospectively in the GPs' medical records for a 15-month follow-up period. Drug prescription data were extracted at the patient level from the GPs' computerized medical records. In the Netherlands, every patient is linked to only 1 GP who collects all medical information, including the use of prescribed medication. Moreover, more than 90% of the GPs use commercially available electronic medical dossiers enabling reliable data collection. Relapse was defined as receiving a benzodiazepine prescription during follow-up. (For details, see Oude Voshaar et al.[11])

In addition to the computerized benzodiazepine prescription records, we assessed patients immediately after they had quit their benzodiazepine use after the first and the second interventions.

The primary variable of interest, benzodiazepine craving, was assessed by means of the BCQ, developed by our research group.[6] The BCQ is a unidimensional, 20-item, self-report questionnaire with good psychometric properties for assessing benzodiazepine craving according to patients' current experience. Sum scores can range from 0 to 20. In a previous report on the BCQ, it was shown that patients who reported craving (sum scores of greater than zero) differed significantly from patients who did not report craving on the BCQ on aspects of dependence severity, psychopathology, negative mood state, and personality.[17]

Additionally, we assessed the use of caffeine, nicotine, and alcohol, and the following self-report questionnaires were administered: to assess severity of benzodiazepine dependence, the Benzodiazepine Dependence Self-Report Questionnaire (Bendep-SRQ)[18,19]; to assess psychological well-being, the 12-item General Health Questionnaire (GHQ-12)[20]; to assess mood, the Dutch shortened version of the Profile of Mood States (POMS)[21]; to assess quality of life, the Medical Outcomes Study Short-Form Health Survey (SF-36)[22,23]; and to assess personality characteristics, the Dutch shortened version of the Minnesota Multiphasic Personality Inventory (NVM).[24]

Analyses

Both patient groups of interest, i.e., the group that had successfully quit after the first minimal intervention and the group that had quit after the additional supervised tapering-off program, were analyzed separately. Since the BCQ sum scores were quite low, we first explored the data by comparing patients who did not report any craving (BCQ sum score = 0) and patients who reported craving to some extent (BCQ sum score ≥ 1), using cross-tabulations.

Predictors of relapse were analyzed separately by means of Cox proportional hazards regression analyses with time to relapse as the dependent variable and each of the following as the independent variable: BCQ sum score (range, 0–20), daily benzodiazepine dosage (dichotomized at 10 mg diazepam equivalent), benzodiazepine half-life (dichotomized at 24 hours), benzodiazepine potency (presence of a 4-aryl group), hypnotic or anxiolytic use (dummy variable defined as self-reported (1) nighttime use, (2) daytime use, or (3) use at both nighttime and daytime), use of antidepressants, use of pain medication, use of psychotropic drugs other than benzodiazepines, and, finally, all variables measured at the baseline assessment. Patients lost to follow-up were analyzed until the moment of loss to follow-up as censored observations. After the univariate Cox proportional hazards regression analyses, variables with a Wald χ^2 statistic of $p < .15$ were entered into a multivariate Cox proportional hazards regression model using a forward, conditional procedure. Crude and adjusted hazard ratios (HRs) with 95% CIs are reported. A p value of $< .05$ was considered significant in the final model. The output of the Cox proportional hazards regression analysis was checked for instability by influential cases and for violation of the proportional hazards assumption. We used SPSS version 10.0 (SPSS Inc, Chicago, Ill.) to perform all analyses.

RESULTS

First Intervention: Discontinuation Letter

Seventy-nine patients who had quit after the discontinuation letter were included in the present analyses. (See Figure 1.) The mean (SD) age of these patients was 63 (13) years, and 68% were female. Patients used benzodiazepines for a mean (SD) duration of 6.9 (7.2) years in a mean (SD) daily dosage of 5.9 (6.0) mg diazepam equivalents.

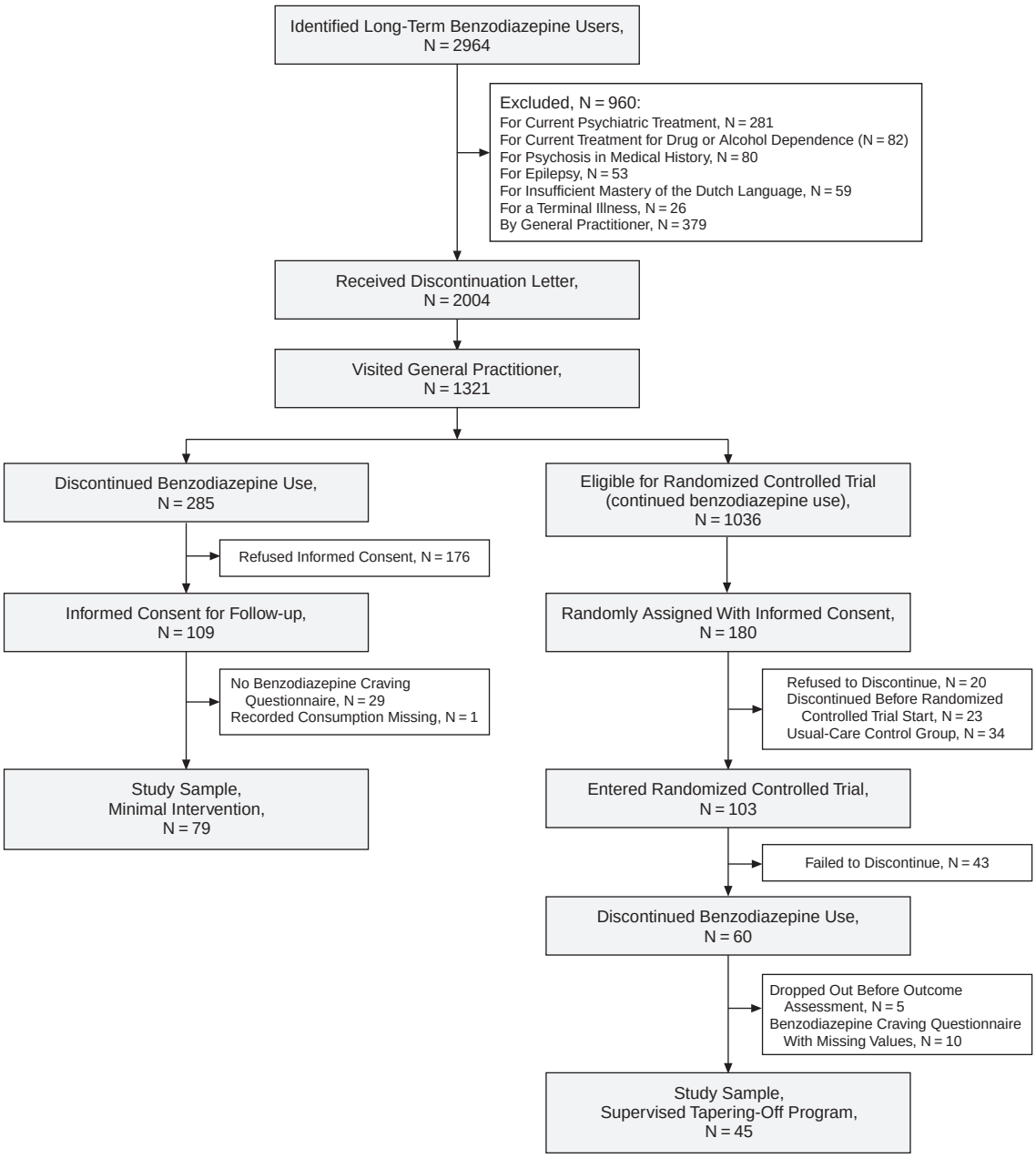
The mean (SD) BCQ sum score was 0.5 (1.0) (quartiles: 0–0–0; range, 0–6). Eighteen patients reported craving to some extent, as indicated by a BCQ sum score of greater than zero. The proportion of relapse did not differ between patients with and without craving (27/61 [44%] vs. 8/18 [44%], p = .99). As shown in Table 1, the BCQ sum score had no predictive value with respect to relapse in the univariate or the multivariate Cox proportional hazards regression analyses (p = .82 and p = .67, respectively).

Second Intervention: Supervised Tapering-Off Program

Of the 180 patients who participated in the randomized, controlled trial, 60 were of interest, as they successfully discontinued their benzodiazepine use with the aid of the tapering-off protocol. Forty-five patients were included for analyses (5 patients withdrew from treatment, and 10 patients provided incomplete data (see Figure 1). Included and excluded patients were comparable with respect to age, gender, benzodiazepine dosage before the start of tapering off, and duration of use (all p value > .18). The mean (SD) age of the 45 participants was 66 (12) years, and 67% were female. Patients used benzodiazepines for a mean (SD) duration of 12.8 (9.5) years in a mean (SD) daily dosage of 7.5 (4.7) mg diazepam equivalents.

The mean (SD) BCQ sum score was 1.2 (2.9) (quartiles: 0–0–1; range, 0–18). Nineteen patients reported craving to some extent, as indicated by a BCQ sum score of greater than zero. The proportion of relapse was higher in patients reporting craving versus patients reporting no craving (13/19 [68%] vs. 11/26 [42%]), a

Figure 1. Patient Recruitment



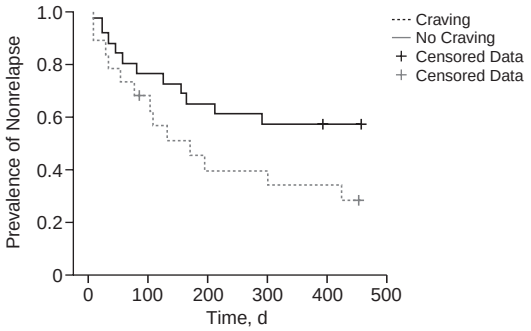
difference that approached significance (p = .08). Figure 2 shows the survival curves for relapse to benzodiazepine use for cravers (BCQ sum score of 1 or higher) and noncravers (BCQ sum score of zero) separately. When corrected for time till relapse by a Cox proportional hazards regression analysis, the BCQ sum score (range, 0–18) was significantly related to relapse (HR = 1.20, 95% CI = 1.07 to 1.36, p = .003). As this result was influenced by one outlier (BCQ sum score = 18, relapse into benzodiazepine use after 11 days), the sum score of this outlier was corrected for on the basis of z scores. Allocation of a z score of 3 yielded a corrected sum score of 10 on the BCQ, thus decreasing the outlier effect yet maintaining the extreme position in the data. The HR of the BCQ sum score remained significant after this correction. (See Table 2: HR = 1.28, 95% CI = 1.07 to 1.55, p = .009.) After correction for other significant independent predictors of relapse, the BCQ sum score still accounted for unique variance (HR = 1.26, 95% CI = 1.02 to 1.54, p = .029).

Table 1. Predictors of Relapse in Successful Quitters After a Minimal Intervention

	Univariate[a]		Multivariate[b]	
Variables	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
BCQ sum score (range, 0–20)	0.82 (0.55 to 1.20)	.82	0.93 (0.65 to 1.32)	.67
Benzodiazepine dosage (> 10 mg)	3.00 (1.43 to 6.27)	.004	4.17 (1.87 to 9.30)	< .001
Duration of benzodiazepine use, y	0.04 (0.00 to 0.77)	.042		
Age, y	1.03 (1.00 to 1.06)	.055		
Stable relationship	0.49 (0.25 to 0.96)	.036		
Living alone	1.93 (0.98 to 3.70)	.057		
Use of alcohol	1.83 (0.92 to 3.58)	.083		
Vitality (SF-36 subscale)	0.99 (0.97 to 1.00)	.054		
Extraversion (NVM subscale)	0.94 (0.88 to 1.01)	.004	0.92 (0.87 to 0.98)	.008

[a]Only the independent variables that had p values < .15 in the univariate regression analyses are shown in the table.
[b]All univariate predictors were entered in the first block, using a forward Wald procedure, after which the BCQ score was added in the second block. Statistics final model: $\chi^2 = 17.2$, df = 3, $p < .001$.
Abbreviations: BCQ = Benzodiazepine Craving Questionnaire, NVM = Nederlandse Verkorte MMPI [Dutch shortened version of the Minnesota Multiphasic Personality Inventory], SF-36 = Medical Outcomes Study Short-Form Health Survey.

Figure 2. Survival Time Until Relapse After Successful Discontinuation



DISCUSSION

This is the first study examining the effect of benzodiazepine craving on relapse after successful discontinuation. We found different results in our 2 groups of interest: in patients able to discontinue on their own after receiving a discontinuation letter, we did not detect any effect of craving on subsequent relapse. However, in long-term benzodiazepine users who needed additional treatment to discontinue successfully (i.e., a supervised tapering-off protocol), a higher extent of craving, as measured with the BCQ, predicted relapse during a 15-month follow-up period, independent of other predictors. This differential effect of craving was probably best explained by population characteristics. Patients who were able to discontinue relatively easily, i.e., with the aid of a discontinuation letter, probably lacked the significant influence of dependence characteristics and therefore experienced hardly any craving, as supported by the low BCQ sum scores and lack of variance herein.

Interpretation of our results is hampered by the lack of previous benzodiazepine relapse studies to compare with. To our knowledge, only 2 studies have specifically examined relapse after successful discontinuation by means of a supervised benzodiazepine tapering-off program, but neither of them included measures of benzodiazepine craving.[13,14] The study of Morin et al.[13] was limited to long-term benzodiazepine users suffering from insomnia (N = 47). They found end-of-treatment insomnia severity and psychological distress as predictors of relapse, analogous to univariate effects of mental health characteristics in our study (the mental health subscale of the SF-36, and the anger, fatigue, and vigor subscales of the POMS). However, in our multivariate model, these characteristics lost significance after correction for age, socioeconomic status, and benzodiazepine dependence severity (Bendep-SRQ lack of compliance subscale), the last of which had not been included by Morin et al.[13] The other study[14] reported a negative association between self-efficacy in coping without benzodiazepine use and relapse after successful, supervised tapering-off, based on a small study of 12 patients with anxiety or insomnia, 3 of whom had relapsed at 3-months' follow-up. In various studies on smoking, higher levels of self-efficacy are consistently associated with decreased craving (e.g., Shadel and Cervone[25] and Dijkstra and Borland[26]), whereas findings from O'Connor et al.[14] appear to be in line with our findings. Similar to our results, Morin et al.[13] and O'Connor et al.[14] did not find an effect of benzodiazepine dosage, suggesting that this variable is only important for achieving successful discontinuation after supervised tapering-off but not in subsequent relapse.[11]

Since the study was conducted in primary care, mainly elderly, low-dose users were included, thereby limiting generalization to high-dose benzodiazepine users. In previous reports on the second step of this study, i.e., the randomized controlled trial, we have shown that the participants were representative of all long-term benzodiazepine users unable to discontinue by themselves after receiving a discontinuation letter, with respect to age, gender, and

Table 2. Predictors of Relapse in Successful Quitters After a Tapering-Off Program

	Univariate[a]		Multivariate[b]	
Variables	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
BCQ sum score (range, 0 to 20)	1.28 (1.07 to 1.55)	.009	1.26 (1.02 to 1.54)	.029
Age, y	1.04 (1.00 to 1.07)	.063	1.06 (1.02 to 1.11)	.007
Insurance status (1 = private; 0 = NHS)	0.43 (0.18 to 1.06)	.068	0.30 (0.11 to 0.77)	.013
Duration of benzodiazepine use, y	1.00 (1.00 to 1.01)	.080		
Problematic use (Bendep-SRQ subscale)	1.37 (0.92 to 2.06)	.125		
Preoccupation (Bendep-SRQ subscale)	1.32 (0.96 to 1.80)	.085		
Lack of compliance (Bendep-SRQ subscale)	6.42 (1.42 to 29.1)	.016	8.25 (1.71 to 39.9)	.009
Withdrawal (Bendep-SRQ subscale)	1.25 (0.97 to 1.60)	.083		
Pain (SF-36 subscale)	0.86 (0.74 to 1.00)	.055		
General health perception (SF-36 subscale)	0.91 (0.84 to 1.00)	.039		
Vitality (SF-36 subscale)	0.92 (0.85 to 1.00)	.039		
Mental health (SF-36 subscale)	0.91 (0.85 to 0.98)	.017		
GHQ-12 sum score	1.15 (0.98 to 1.35)	.091		
Anger (POMS subscale)	1.06 (0.99 to 1.13)	.099		
Fatigue (POMS subscale)	1.06 (1.00 to 1.12)	.044		
Vigor (POMS subscale)	0.93 (0.86 to 1.00)	.048		
Shyness (NVM subscale)	0.95 (0.89 to 1.01)	.080		
Extraversion (NVM subscale)	1.08 (1.00 to 1.16)	.039		

[a]Only the independent variables that had p values < .15 in the univariate regression analyses are shown in the table.
[b]All univariate predictors were entered in the first block, using a forward Wald procedure, after which the BCQ score was added in the second block. Statistics final model: $\chi^2 = 22.6$, df = 4, $p < .001$.
Abbreviations: BCQ = Benzodiazepine Craving Questionnaire, Bendep-SRQ = Benzodiazepine Dependence Self-Report Questionnaire, GHQ-12 = 12-item General Health Questionnaire, NHS = National Health Service, NVM = Nederlandse Verkorte MMPI [Dutch shortened version of the Minnesota Multiphasic Personality Inventory], POMS = Dutch shortened version of the Profile of Mood States, SF-36 = Medical Outcomes Study Short-Form Health Survey.

benzodiazepine dosage. (See Oude Voshaar et al.[4] for details and discussion.) Nevertheless, even if our recruitment process has led to significant selection bias, this bias is probably comparable to clinical practice in which only the most motivated patients will be referred for benzodiazepine discontinuation treatment.

The concept of low-dose benzodiazepine dependence has been criticized by some researchers, mainly for 2 reasons: (1) the number of benzodiazepine users who escalate their dosage beyond therapeutic levels is low,[27] and (2) long-term, low-dose benzodiazepine usage is considered as "normal physical dependence" necessary for the long-term treatment of chronic anxiety and should, therefore, not be considered abuse or addiction.[28] Advocates of the concept of low-dose benzodiazepine dependence emphasize that (1) the withdrawal syndrome for benzodiazepine includes unique symptoms that can be distinguished from rebound anxiety,[29] (2) withdrawal symptoms are identical for low-dose and high-dose users,[30] and, finally, (3) approximately half of all low-dose users fulfill DSM-III-R criteria for dependence.[3] Our results contribute to these latter arguments by showing that craving, a concept specifically associated with the use of addictive substances, predicts relapse after successful discontinuation of low-dose benzodiazepine usage.

Our findings point to a potentially important role for craving in subsequent relapse after successful benzodiazepine discontinuation, but only for the subgroup of low-dose benzodiazepine users who need specific treatment for benzodiazepine discontinuation in clinical practice. If these results hold true in subsequent studies, they should guide relapse prevention programs, including treatment elements with a focus on coping with craving experiences.

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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